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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/080,866	02/22/2002	Eriks Sasha Paegle	P1732R1	9791

9157 7590 03/25/2005

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EXAMINER	
RIGGINS, PATRICK S	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 03/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/080,866	PAEGLE ET AL.	
	Examiner	Art Unit	
	Patrick S. Riggins	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 February 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Information Disclosure Statement

1. Applicants are requested to resubmit the information disclosure statement mailed 5/20/02. Either the scanning or printing has led to a faint and nearly illegible listing of references. Examiner was able to glean the necessary information from the IDS, and as such the references have been considered, however if this application leads to a patent, the publisher would be unlikely to be able to sufficiently interpret the references presented on this IDS and as such would be unable to provide a true prior art listing in the published patent. Applicant's cooperation in this matter is greatly appreciated.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

4. Claim 1 is drawn to vector for producing a heterologous polypeptide in a prokaryotic cell. As used in the instant application, vector is intended to mean a plasmid. Claim 1 requires that the vector comprise "RNA encoding the polypeptide." As a plasmid is constructed of DNA, it is unclear what is intended by saying the vector contains RNA. For the purposes of examination, it will be assumed that the applicants intend to refer to DNA that may be expressed and encodes

the polypeptide. As claims 2-5 depend from claim 1 and dependent claims are construed to include all the limitations of the parent, claims 2-5 are similarly found to be vague and indefinite.

5. Claim 6 is drawn to a process of producing a heterologous polypeptide comprising culturing cells that comprise "RNA encoding the polypeptide with a non-lambda promoter therefor." As RNA is an expression product of gene that contains a promoter, and the RNA itself does not have a promoter, it is unclear what is fully intended by this limitation. For the purposes of examination, this will be read that the RNA is expressed from a gene with a non-lambda promoter. As claims 7-22 all depend from claim 6, they are similarly found to be vague and indefinite.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1 and 3 are rejected under 35 U.S.C. 102(b) as being anticipated by Hasan. The claims are drawn to a vector comprising anti-termination nucleic acid with a non-lambda promoter and a recognition site for binding to the anti-terminator protein encoded by the nucleic acid located 5' to the polypeptide-encoding portion of the vector for expression in prokaryotic cell, optionally bacterial cells. Hasan discloses (see Figures 1 and 2) plasmids designed for the expression of proteins in prokaryotic cells comprising either a Plac or Ptac promoter, a nutL site,

the N gene, and a gene of interest. The exemplified gene is galK. These vectors are designed to express the protein of interest in E. coli cells.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hasan in view of Hsu (of record). Hasan discloses a vector comprising anti-terminator nucleic acid that acts on a non-lambda promoter-driven heterologous gene, with an RNA recognition site for binding the antiterminator protein, 5' to the heterologous gene, as described above. Hasan does not disclose a vector further encoding GreA or GreB. Hsu discloses plasmids that express GreA and GreB and shows they are functional in increasing the expression of the CAT gene (Figure 3). As the goal of both Hasan and Hsu was to allow for the high-level expression of proteins, one would have been motivated to construct a vector comprising both nut site and N gene of Hasan and GreA or GreB as taught by Hsu. Thus it would have been obvious to one of ordinary skill in the art at the time of filing to create a vector comprising the nut antiterminator system and GreA or GreB to promote efficient transcriptional elongation and prevent unnecessary pauses.

10. Claims 1, 3-4, 10, 12-15, and 17-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hasan in view of Li or Clements. Hasan teaches of a plasmid that bears all of the characteristics as delineated in claim 6, as defined above pertaining to the vector of claim 1.

Additionally, the plasmids that Hasan teaches are designed to express the N gene and the protein of interest as a polycistronic message. Hasan dos not disclose the production and purification of the protein of interest. Additionally, Hasan does not specifically disclose that the polypeptide is optionally eukaryotic, mammalian, human, or thrombopoietin (TPO) or fibroblast growth factor-5 (FGF-5). Li and Clements both teach the well-known process of expressing and purifying a protein of interest in E. coli. Li teaches of the expression and purification of TPO from cytoplasmic inclusion bodies, while Clements teaches of the expression and purification of FGF-5 also from the cytoplasm of bacterial cells. Additionally, as the constructs are naturally configured in Hasan and Li or Clements, the N gene and the protein of interest are expressed from separate promoters, so subcloning to combine the vectors of Li or Clements with the vector of Hasan, would produce a vector with two independent promoters. As the purpose of the vector of Hasan was to allow for the high level expression of a protein in bacterial cells, Li and Clements both teach a different protein that is expressed and purified in bacterial cells, and the skilled artisan always wants high level expression of the protein to be purified, one would have been motivated to produce and purify proteins, specifically TPO or FGF-5 as taught by Li or Clements, respectively, using the plasmid expression system of Hasan. Thus, it would have been obvious to one of ordinary skill in the art to us the plasmid system of Hasan to produce and purify TPO or FGF-5 as taught by Li or Clements, respectively.

11. Claims 1 and 3-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hasan and Li in further view of Makrides (of record). Claim 11 depends from claim 6 and Hasan and Li together teach the limitations of claim 6 as described above. Neither Hasan nor Li teach of the use of the trp or the alkaline phosphatase promoter nor of purification of the protein of interest

from the culture supernatant. Makrides teaches (see Table 1 and pp 513-515) a variety of promoters that can be used for protein expression in bacteria. Among them are the lac and tac promoters used by Hasan, as well as the trp and alkaline phosphatase (phoA) promoters. The skilled artisan would have been motivated to use either the trp or phoA promoters because both lac and tac promoters require IPTG for induction and on a large scale, IPTG induction can be a costly proposition. The trp and phoA promoters are induced simply through starvation of either tryptophan or phosphate, respectively, which is a much less costly means of induction (see Table 1 and page 514). Additionally, Makrides teaches of expression of a protein of interest such that it is secreted into the culture supernatant (see Table 3, p 520 and p 521). One of skill in the art would have been motivated to design the vector for expression of the protein of interest to secrete the protein of interest into the culture supernatant because extracellular expression leads to the least level of proteolysis and a simpler purification scheme (see Table 2). Thus, it would have been obvious to one of ordinary skill in the art to use a trp or phoA promoter and to express the protein of interest such that it would be secreted into the culture medium as taught by Makrides in the plasmids of Hasan using the expression and purification methods of Li.

12. Claims 1-4, 6-10, 12-15, and 17-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hasan and Hsu as applied to claim 2 above, and further in view of Li. Together Hasan and Hsu teach of a vector that comprises an N gene, a protein of interest, and either GreA or GreB. Hasan and Hsu do not teach the expression and purification of the protein of interest nor the expression of a mammalian polypeptide. As described above, Li teaches the well-known methods of expression and purification of human TPO. The skilled artisan would have been motivated and have found it obvious to combine the teachings of Hasan, Hsu, and Li

to express and purify a protein of interest using both the antitermination system combined with the GreA/GreB system because both the antitermination system of Hasan and the Gre system of Hsu lead to an increase in production of the protein of interest.

13. Claims 23-32 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Li or Clements in view of Hsu. Li discloses a vector for the expression of human TPO in bacterial cells and a process for producing and purifying the TPO from inclusion bodies of the bacterial cytoplasm. Similarly, Clements discloses a vector for the expression of human FGF-5 in bacterial cells and a process for producing and purifying the FGF-5 from the cytoplasm of the bacteria. Neither vector in Li nor Clements contain nucleic acid encoding GreA or GreB. Hsu discloses a plasmid for expressing GreA or GreB and a process for enhancing the expression of a gene of interest through expression of GreA or GreB (see Figure 3). One would have been motivated to combine the teachings of Li or Clement with those of Hsu because in production of a protein of interest for the purification of that protein, one desires to have the greatest level of expression of that protein possible. Hsu teaches that both GreA and GreB can lead to up to an eight-fold induction of expression of a gene of interest (see p. 11590, column 2). Thus, it would have been obvious to one of ordinary skill in the art to construct and use vector combining GreA or GreB expression with the gene for expressing the protein of interest.

14. Claims 23-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Li or Clements and Hsu as applied to claims 23-32 and 34 above, and further in view of Makrides. Li or Clements combined with Hsu teaches the limitations of claim 27 as taught above. Li or Clements and Hsu do not teach the use of trp or phoA promoters and do not teach of the purification of the protein of interest from the culture supernatant. As described above in

reference to claim 11, Makrides teaches of the use of a trp and phoA promoter and of the methods for and usefulness of protein secretion. One would have been motivated to use either a trp or phoA promoter and design the system for secretion of the protein of interest for the reasons supplied above in paragraph 10. Thus, it would have been obvious to one of skill in the art to use a trp or phoA promoter in the combined expression and purification system of Li and Hsu further modifying the system for secretion of the supernatant into the culture supernatant.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patrick S. Riggins whose telephone number is (571) 272-6102. The examiner can normally be reached on M-F 7:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Patrick Riggins, Ph.D.
Examiner
Art Unit 1636

JAMES KETTER
PRIMARY EXAMINER